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INTELLECTUAL
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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and Complete Specification filed on 05/03/2004 in respect of Patent Application No. 281/MUM/2004 of **(a) M/S. IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India (c) Indian company incorporated under the Companies Act 1956.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this day of July 2005.

(A.T. PATRE)
ASSTT. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
[See section 5 (2), 7, 54 and 135; rule 39]

1. We,

   (a) M/S. IPCA LABORATORIES LIMITED

   (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

DUPLICATE

2. Hereby declare –

   (a) that we are in possession of an invention titled **"Improved process for resolution of (±) methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetra hydro thieno [3,2-c] pyridin-5-yl) acetate"**

   (b) that the Complete Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) Kumar, Ashok

   (b) B/203, 204, Sterling Co. Hsg. Soc.
   A2-A3, Sundarban Complex,
   Andheri (West)
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   (c) Indian National

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   (d) Indian National

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– 5 MAR 2004

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Maharashtra, India
(c) Indian National

(a) Burudkar, Sandeep Madhavrao
(b) Survey No. 17/A, Harinagar,
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Maharashtra, India
(c) Indian National

(a) Shah, Chirag Hasmukh
(b) D/704, Bhakti Complex,
Link Road, Dahisar(West)
Mumbai-400 068
Maharashtra, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kumar, Ashok)

(Vyas, Ketan Dhansukhlal)

(Barve, Govind Sanjay)

(Bhayani, Priti Jayesh)

(Nandavadekar, Sanjay)

(Burudkar, Sandeep Madhavrao)

(Shah, Chirag Hasmukh)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.
8. Following are the attachment with the application:
   (a) Complete specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) copy Form 26 (Original Power of Attorney in our favour has been submitted with application number 150/MUM/2003)
   (d) Fee Rs.3000/- in cheque bearing No. 666413 dated 19th Feb, 2004 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 20th day of Feb 2004

Dr. Gopakumar G. Nair
Agent for the Applicant
Gopakumar Nair Associates
Nair Baug, Akurli Road, Kandivli (East),
Mumbai – 400 101, Maharashtra, India

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

COMPLETE SPECIFICATION

[See section 10; rule 13]

"Improved process for resolution of (±) methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetra hydro thieno [3,2-c] pyridin-5-yl) acetate"

DUPLICATE

(a) IPCA LABORATORIES LIMITED

(b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

The following specification describes the nature of this invention and the manner in which it is to be performed:

Field of invention:

The present invention relates to a process for isolation of dextro rotatory enantiomer (+)-(S)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) acetate from racemic compound using mixture of solvents.

Background and Prior Art:

The compound methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno [3,2-c] pyridin-5-yl) acetate also known by the international non-proprietary name (INN) as Clopidogrel is well known for its platelet aggregation inhibition properties.

The platelet inhibiting activity of Clopidogrel makes it an effective drug for reducing the incidence of ischemic strokes, heart failures and chances of arterial blockings.

The patent E.P.0099802 (Sanofi, S.A. 1984) describes a process for the synthesis of racemic mixture (±) methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno [3,2-c] pyridin-5yl) acetate by reaction of methyl-2-chloro-(2-chlorophenyl) acetate with 4,5,6,7-tetrahydrothieno [3,2-c] pyridine to get free base. The racemic mixture is isolated in the form of hydrochloride salt of (±) methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno [3,2-c] pyridin-5-yl) acetate.

The patent E.P.0281459 (Sanofi, S.A. 1988) relates to the process for resolution of racemic mixture made as per prior art E.P.No.099,802 (Sanofi, S.A. 1984). The free base of racemic mixture is dissolved in acetone and reacted with levo-camphor-10-sulphonic acid. The diasteriomeric salt which separates out was filtered, and purified by refluxing, cooling and filtration from acetone. The process of purification in acetone is repeated in case the desired purity of diasteriomeric salt is not achieved.

The patent application US 2002/0177712 A1, (Cadila Healthcare Ltd.) describes a

process for resolution of racemic mixture of free base by dissolving free base in solvents like acetone, water & ethyl acetate and mixture thereof which is reacted with levo-camphor -10-sulphonic acid and isolating the desired diasteriomer by filtration. The desired optical purity of diasteriomer is achieved by purification from solvents like acetone.

From the prior art it is evident that the racemic (±)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) acetate resolved by converting it to the corresponding levo-camphor-10-sulphonic acid using suitable solvent or mixture of solvents such as water, acetone & ethyl acetate, wherein the required diasteriomeric salt separates out, which on purification from solvents like acetone gives the required diasteriomeric salt. The product of desired purity, however, is achieved by repeated purifications using solvents such as acetone, which results in to lower yields and increased costs. It had always been a desire to obtain methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) acetate of higher enantiomeric purity, with a higher yield and lower cost.

The present invention overcomes the problems of the prior art for resolution of racemic mixture of (±)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) acetate. The racemic mixture is reacted with levo-camphor-10-sulphonic acid to form mixture of corresponding diasteriomeric salts, in mixture of solvents, thereby the desired diasteriomeric salt of methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5yl) acetate separates out to give a product of desired optical purity and requiring no further purification leading to higher yields & low cost.

Objective of the invention:

The main objective of the present invention is to develop a process for obtaining dextro rotatory enantiomer(+)-(S)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2 c]pyridin-5-yl) acetate which is cost effective, eliminates the need of repeated crystallization, have desired enantiomeric purity and higher yield.

The summary of the invention:

The present invention discloses a process for resolution of racemic (±)methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) acetate to get dextro rotatory enantiomer (+) (S)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl) using anhydrous levo-camphor-10-sulphonic acid in mixture of solvents.

Detailed description of the invention:

The present invention describes the process of resolution for racemic (±)-methyl-2-(2-chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno[3,2-c]pyridin-5-yl) acetate.

According to the present invention the recemic mixture of free base of (±)-methyl-2(2-chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno[3,2-c]pyridin-5-yl) acetate is subjected to resolution by forming the diasteriomeric salts using levo-camphor-10- sulphonic acid salt in a mixture of solvents, which allows to crystallize out the camphor sulphonic acid salt of dextro enantiomer by leaving behind camphor sulphonic acid salt of levo enantiomer in the mother liquor. A simple filtration of the reaction mass gives the desired diasteriomer of high purity without subjecting to any further purification.

The solvents of choice were the group of solvents like acetone, dichloromethane, toluene and cyclohexane. The mixtures of solvents used were acetone: dichloromethane, acetone: toluene and acetone: cyclohexane, wherein the preferred mixtures of the solvents were acetone: dichloromethane and acetone: toluene and the most preferred mixture of the solvents is acetone: dichloromethane. The preferred ratio of the solvents used is 20: 0.5, wherein the more preferred ratio is 15: 0.75 and the most preferred ratio is 10: 1. The anhydrous levo-camphor-10-sulphonic acid is used in the most preferred molar ratio of 1.05 to 1.1 to the racemic mixture. The salt formation is carried out in the temperature range of 25 - 35°C, wherein the most preferred temperature range is 30±2°C.

The salt formation were carried out by suspending the racemic mixture of (±) methyl-2-(2chlorophenyl)-2-(4,5,6,7 -tetrahydrothieno [3,2-c] pyridin-5-yl) acetate in the mixture of solvents of acetone and dichloro methane in the ratio of 10:1 adding levo-camphor-10-sulphonic acid at 30± 2°c, and stirring at 30± 2°c for 12-15 hours.

The crystalline salt of dextro rotatory enantiomer methyl -2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate camphor-10-sulphonic acid which separated out is cooled in the range of -5 to 10°C, wherein the most preferred temperature range is -2 to 3°C. This temperature range is critical to obtain higher yields of the desired isomer. Increase of temperature to higher than the range of - 5 to 10°C leads to lowering of yield and increase in the costs.

The crystalline salt is filtered and washed with suitable solvent like acetone and dried under vacuum below temperature of 50°C. The yield of dextro rotatory enantiomer methyl 2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate camphor-10sulphonic acid salt is obtained in the range of 76.0 - 80% (of stoichemetric).

The enantiomeric purity of the dextro rotatory enantiomer is NLT 99.5% by High Pressure Liquid Chromatography using suitable chiral column.

By using resolution process mentioned in the prior art, the enantiomeric purity of (+) - methyl -2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate was 96%.

Thus, it can be seen that following the present invention, the enantiomeric purity of (+) - methyl -2- (2-chlorophenyl)-2-(4,5,6, 7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate camphor-10-sulphonic acid salt is more than 99.5%, without subjecting it to repetitive crystallization as mentioned in the prior art. The enantiomeric purity obtained by following the process of the prior art was 96% for dextro enantiomer.

The salt of (+) - methyl -2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate camphor-10-sulphonic acid with high enantiomeric purity is then converted to free base by conventional process by basification using sodium bicarbonate in water as media. The free base is then extracted using solvent like dichloromethane. The free base obtained as residue after evaporation of solvent is then converted into bisulphate salt by conventional process.

The following example are given for the purpose of illustrating the invention and do not limit the present invention to the examples.

Example-1

93.0 gm (0.28 mole) of racemic base methyl-2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate is charged in 550 ml mixture of acetone and dichloromethane solvent. 73.8 gm (0.31 mole) levo-camphor-10-sulphonic acid is added to the solution. The clear solution is stirred overnight at 30±2°C. The reaction mass is cooled to -2 to 3°C. The crystals obtained is filtered and washed with acetone and dried under reduced pressure. The yield obtained is 76.0% on the basis of the starting racemate charged. The crystals have $[\alpha]_D20$ +25.25; HPLC assay = 99.65%.

Example-2

93.0 gm (0.28 mole) of racemic base methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate is charged in 550 ml mixture of acetone and dichloro methane solvent. 40.31 gm (0.17 mole) levo-camphor-10-sulphonic acid is added to the solution. The clear solution is stirred overnight at 30±2°C. The reaction mass is cooled to -2 to 3°c. The crystals obtained is filtered and washed with acetone and dried under reduced pressure. The yield obtained is 66-68% on the basis of the starting racemate charged. The crystals have $[\alpha]_D20$ +25.9; HPLC assay = 99.641%.

Example-3

93.0 gm (0.28 mole) of racemic base methyl-2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate is charged in 550 ml mixture of acetone and toluene. 73.8 gm (0.31 mole) levo-camphor-10-sulphonic acid is added to the solution. The clear solution is stirred overnight at 30±2°c. The reaction mass is cooled to -2 to 3°c. The crystals obtained is filtered and washed with acetone and dried under reduced pressure. The yield obtained is 80% on the basis of the starting racemate charged. The crystals have $[\alpha]_D20$ +24.49 ; HPLC assay = 99.285%.

Example-4

93.0 gm (0.28 mole) of racemic base methyl-2-(2-chlorophenyl)-2-(4,5,6,7 - tetrahydrothieno [3,2-c] pyridin-5-yl) acetate is charged in 550 ml mixture of acetone and dichloro methane. 73.8 gm (0.31 mole) levo-camphor-10-sulphonic acid is added to the solution. The clear solution is stirred overnight at 30 ±2°c. The reaction mass is cooled to 5 - 10°c. The crystals obtained is filtered and washed with acetone and dried under reduced pressure. The yield obtained is 66% on the basis of the starting racemate charged. The crystals have $[\alpha]_D20$ +25.5; and HPLC assay = 99.64%

Example: 5

93.0 gm (0.28 mole) of racemic base methyl-2- (2-chlorophenyl)-2-(4,5,6,7-tetrahydro thieno [3,2-c] pyridin-5-yl) acetate is charged in 550 ml mixture of acetone and cyclohexane solvent. 73.8 gm (0.31 mole) levo-camphor-10-sulphonic acid is added to the solution. The clear solution is stirred overnight at 30±2°C. The reaction mass is cooled to -2 to 3°C. The crystals obtained is filtered and washed with acetone and dried under reduced pressure. The yield obtained is 76.0% on the basis of the starting racemate charged. The crystals have $[\alpha]_D20$ +24.668; and HPLC assay = 99.792%.

WE CLAIM,

1. An improved process for resolution of racemic mixture of methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (Clopidogrel) (I), wherein the said process comprises

a) suspending the racemic mixture of methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (Clopidogrel) (I) in mixture of solvents;

b) adding levo-camphor-10-sulphonic acid at 25-35°C to the said mixture;

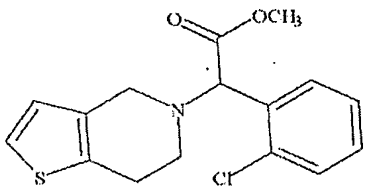
c) stirring the said mixture between the said temperature range of 25-35°C for 12-15hours to obtain camphor sulphoic acid salts of racemic mixture of (I);

d) cooling the said mixture to temperature range of -5 to 10°C to separate out dextro enantiomer of camphor sulphonic acid salt of racemic mixture of (I);

e) separating the crystalline salt of dextrorotatory enantiomer of methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate camphor sulphonic acid by filtering the said mixture;

f) washing the said crystalline salt with suitable solvent like acetone; and

g) drying the product under vacuum below temperature of 50°C.



[I]

2. An improved process for resolution of racemic mixture of methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as

claimed in claim 1 (a), wherein, the said mixture of solvent is polar and non polar solvent.

3. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein, the said mixture of polar and non-polar solvents are acetone, methylene chloride, toluene, cyclohexane.
4. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein the said mixture of polar and non-polar solvents are in the ratio of 20:0.5.
5. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7- tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein the said mixture of polar and non polar solvents are in the ratio of 10:1.
6. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7- tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein the said mixture of polar and non-polar solvents are acetone and dichloromethane.
7. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7- tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein the said mixture of polar and non polar solvents are acetone and toluene.
8. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7- tetrahydro theino[3,2-C] pyridine-5-yl acetate (I)as claimed in claim 1, wherein the said mixture of polar and non polar solvents are acetone and cyclohexane.
9. An improved process for resolution of racemic mixture methyl-2-(2-chlorophenyl-2-(4,5,6,7- tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) as claimed in claim 1, wherein, the preferred molar ratio of anhydrous levo-camphor-10- sulphonic acid to racemic mixture is 1.05 to 1.1

10. An improved process for resolution of (I) methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate as claimed in claim 1, wherein, the most preferred temperature range for salt formation is 30±2°C.
11. An improved process for resolution of (I) methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate as claimed in claim 1, wherein the said dextrorotatory enantiomer of the said camphor sulphonic acid salt of methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate (I) is separated out at temperature -2 to 3°C
12. An improved process for resolution of (I) methyl-2-(2-chlorophenyl-2-(4,5,6,7-tetrahydro theino[3,2-C] pyridine-5-yl acetate as substantially described herein with reference to the foregoing examples 1 to 5.

Dated this 20th Day of Feb 2004

Dr. Gopakumar G. Nair
Agent for the Applicant